The Efficacy and Safety of Intralesional Immunotherapy with Measles, Mumps, Rubella Virus Vaccine for the Treatment of Common Warts in Adults

Pushpinder Singh Chauhan,
Vikram K. Mahajan,
Karaninder Singh Mehta,
Ritu Rawat,
Vikas Sharma

Department of Dermatology, Venereology and Leprosy, Dr. R. P. Govt. Medical College, Kangra (Tanda), Himachal Pradesh, India

Abstract

Background: Most therapeutic modalities for common warts remain unsatisfactory. **Objectives**: To evaluate efficacy and safety of intralesional MMR (measles, mumps, rubella virus) vaccine in the treatment of common warts in adults. **Patients and Methods**: There were 110 (M:F = 61:49) patients aged 19–62 years having 1–211 warts over dorsal hands, feet, palms, soles, and periungual skin for 1–252 months. MMR vaccine 0.25 mL was injected intralesionally in the largest wart and repeated at 2-week interval until complete clearance or maximum of five doses. The outcome was evaluated as complete clearance, excellent, good, or unsatisfactory response on visual analog scale at every visit and at 4 and 8 weeks, thereafter by comparing baseline clinical photograph. Likert scale was used for patient satisfaction level assessment similarly. **Results:** Only 51 patients completed the study and 42 (82.4%) of them showed complete clearance of warts and 9 (17.6%) patients showed good or unsatisfactory response. In 4 (7.8%) patients, the warts subsided completely after one dose itself. The four patients showing excellent response after five doses initially also continued to improve during follow-up period of 8 weeks. Except for injection site pain, no adverse effects were noted. There was no recurrence of warts among cured who were also very much satisfied from treatment. **Conclusion:** Despite variable results, intralesional MMR vaccine immunotherapy appears another possible safe and effective treatment option for common warts in a set of adult patients with advantages of regression of distant warts, no significant adverse effects and low recurrence. However, well-designed, controlled studies for minimum effective dose and treatment schedule are highly desirable to make any recommendation.

Keywords: *Human papilloma virus, immunotherapy, verruca vulgaris, warts*

Introduction

Common warts or verruca vulgaris are hyperkeratotic papillomas due to human papilloma virus (HPV) infection. They frequently occur over hands of children and young adults but may be located on any cutaneous or mucosal surface. Although spontaneous recovery occurs, it usually takes a long time and even years. However, there is a little tendency for spontaneous healing among few patients in long-term follow-up requiring active intervention. Destructive procedures such as cauterization with salicylic acid, podophyllotoxin, trichloroacetic acid (TCA), formaldehyde, 5-flurouracil, and photodynamic therapy, or surgical methods like cryosurgery, laser ablation, electrocautery, and excision are used invariably to treat warts. They are usually painful, often cause scarring and show inconsistent outcome with high frequency of relapse. Treatment with contact sensitizers, imiquimod, intralesional interferons and oral levamisole, cimitidine, or zinc sulfate has been tried with variable success.[1-4] Recently, immunotherapy with intralesional antigens (autogenous vaccine, candida antigen, mumps antigen, trichophytin skin test antigen, tuberculin) or vaccines (BCG vaccine, measles, mumps, rubella virus or MMR vaccine, *Mycobacterium w* vaccine) has been tried for the treatment of common warts with encouraging results.[5,6] Although not well elucidated, intralesional MMR immunotherapy perhaps employs the ability of the immune system to recognize viral antigens that induces a delayed-type hypersensitivity reaction not only to the antigen but also against the HPV, thereby

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Address for correspondence:
Dr. Vikram K. Mahajan, Department of Dermatology, Venereology and Leprosy, Dr. R. P. Govt. Medical College, Kangra (Tanda), Himachal Pradesh, India.
E-mail: vkm1@rediffmail.com

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increasing the ability of the immune system to recognize and clear HPV.[7] Consequent to this, the stimulated immune response clears all lesions on other body sites along with locally treated lesions.[5] Immunotherapy using intralesional MMR vaccine has been found useful in treating common warts particularly in children.[8-10] We evaluated the efficacy and safety of MMR vaccine in the treatment of common warts in adults.

Patients and Methods

The study enrolled 110 adults diagnosed with common warts for the study after informed written consent. Demographic and clinical details for number and size of warts and sites involved were recorded. Photographic records were made prior to treatment (at baseline) and at each subsequent visit. No other treatment for warts was allowed for concurrent use. Pregnant and lactating women; children <12 years; patients with apparent infection or immune suppression, asthma, allergic skin disorders, meningitis, or convulsions; or who have received treatment for warts during last 1 month were excluded. The study was approved by the Institutional Protocol Review Board and Institutional Ethics Committee.

Treatment protocol and outcome evaluation

Freeze-dried MMR vaccine (Tresivac) single use vials marketed by Serum Institute of India Ltd. Mumbai, India, stored at 2°C–8°C were purchased when needed. The vaccine was reconstituted with 0.5 mL of provided diluent (distilled water) as per manufacturer's instruction immediately before intralesional use. All enrolled patients received intralesional injection of 0.25 mL of reconstituted MMR vaccine in largest wart with 30G insulin syringe (one dose). The unused vaccine was discarded. The dose was repeated at every 2-week interval in a similar fashion until complete clearance or for a maximum of five doses.

The patients were evaluated clinically and by comparing with baseline clinical photographic records at each treatment session for resolution of treated wart and distant warts, reduced size and number of warts, and any immediate or late adverse effects, if any. The clinical improvement was rated as complete clearance, excellent response, good response, or unsatisfactory response by the patient and physician global assessment using visual analog scale score at each visit taking baseline clinical photograph as controls [Table 1]. After completion of treatment period, the patients were also followed up similarly every 4-week interval for another 8 weeks. The patient satisfaction level was assessed on Likert scale at the end of the study period [Table 1].

Results

The baseline characteristics of study subjects are tabulated [Table 2]. There were 61 men and 49 women (M:F = 1.2:1) aged between 19 and 62 (mean ± SD: 31.3 ± 11.15) years having 1–211 (mean ± SD: 19.8 ± 29.27) warts for 1–252 (mean ± SD: 31.7 ± 41.67) months. The majority 81 (73.6%) patients were aged between 21 and 40 years. One patient had maximum 211 warts. These were localized mainly over dorsal hands and feet (74 patients), and palms/soles (29 patients), periungual skin (1 patient), and multiple sites including hands and face (6 patients). Some of the patients had received treatment in the past with paring and cauterization with TCA without benefit. Fifty-nine patients dropped out from follow-up at various stages of study citing complete dissatisfaction (score on Likert scale = 1) from therapy, 24 patients, the majority, dropped out at 4 weeks after fifth treatment session.

Table 3 depicts therapeutic outcome in 51 patients who completed the study; overall 42 (82.4%) patients had complete clearance of warts and 9 (17.6%) patients showed partial (good to unsatisfactory response) response at end

Table 1: Evaluation of clinical improvement and patient satisfaction level at end of study period

Grades of clinical improvement	Definition	Number of patients who completed the study period (*n*=51) (%)
Complete clearance (VAS score=100%)	Complete disappearance of warts including distant ones and skin texture at the site is restored to normal	42 (82.4)
Excellent response (VAS score=75%-99%)	Reduction in size and number including distant ones and few residual warts still visible	0
Good response (VAS score=50%-74%)	Some reduction in size only including that of distant ones but no decrease in number of warts	2 (3.9)
Poor response (VAS score ≤50%)	No significant change in size and number of warts	7 (13.7)
Recurrence	Recurrence during the study period	Nil
Patient satisfaction level	**Score on Likert scale**	**Number of patients who completed the study period (*n*=51)**
Very much satisfied	5	42
Somewhat satisfied	4	-
Undecided	3	2
Not really satisfied	2	7
Not at all satisfied	1	59

VAS=Visual analogue scale

of study period. The majority 12 of 25 (48%) patients had complete clearance of warts after five doses and after three doses in 11 of 73 (15%) patients [Figures 1-6]. In four (7.8%) patients, the warts subsided completely after one dose itself. The four patients showing excellent response after five doses initially also continued to improve during follow-up period of 8 weeks after the fifth dose. The two patients remained undecided (score on Likert scale = 3), and other seven patients were not really satisfied (score on Likert scale = 2) from treatment. All patients reported mild-to-moderate injection site pain at the time of intralesional injection but none discontinued the treatment. No systemic adverse effects, residual scarring or pigmentation, adverse effect on nail growth, onycholysis, or nail dystrophy were noted. There was no recurrence of warts at the end of study period among cured who were also very much satisfied (score on Likert scale = 5) from treatment.

Table 2: Baseline characteristics of patients

Baseline characteristics	Number of patients (*n*=110) (%)
Gender	
Men	61 (55.5)
Women	49 (44.5)
Men:women	1.2:1
Age (years)	
Range, mean±SD	19-62 (31.3±11.15)
<20	9 (8.2)
21-40	81 (73.6)
41-60	18 (16.4)
>60	2 (1.8)
Number of warts	
Range, mean±SD	1-211 (19.8±29.27)
1-10	57 (51.8)
11-20	25 (22.7)
21-30	13 (11.8)
>30	15 (13.7)
Duration in months	
Range, mean±SD	1-252 (31.7±41.67)
1-12	52 (47.3)
13-24	25 (22.7)
25-36	9 (8.2)
37-48	7 (6.4)
49-60	3 (2.7)
>60	14 (12.7)
Sites of warts	
Dorsal hands/feet	74 (67.2)
Palmoplantar	29 (26.4)
Periungual skin	1 (0.9)
Multiple sites*	6 (5.5)

*Included patients having lesions over dorsal hands, feet, palms and face. SD=Standard deviation

Discussion

A multitude of therapies for common warts reflects that no single treatment has proven 100% efficacy and most of them remain unsatisfactory. An uncontrolled proliferation of warts, both common and genital, in HIV-infected patients with high viral loads and low T-lymphocyte cell counts, rapid proliferation of warts in organ transplant recipients, occurrence of innumerable flat warts in patients with epidermodysplasia verruciformis, and a significant epidermal and dermal influx of CD4 + lymphocytes in spontaneously regressing warts suggests the immune system, particularly the cell-mediated immunity plays a significant role in pathogenesis and persistence of warts.[11,12] This conceptualized intralesional immunotherapy using different antigens to stimulate cell-mediated and humoral immunity and accelerated clearance of virus and viral infected cells leading to clearing of intralsionally treated and distant

Table 3: Treatment outcome and follow up for therapeutic outcome, recurrences and long term adverse effects

Follow up	Number of patients lost to follow up	Number of patients (%)				Remarks
		Poor response (VAS Score ≤50%)	Good response (VAS Score=50%-74%)	Excellent response (VAS Score=75%-99%)	Complete clearance (VAS Score=100%)	
Day - 0 (*n*=110)	All patients received 0.25 ml of MMR vaccine injected in the largest wart and every 2 weekly interval thereafter until complete clearance or for maximum of 5 doses. They were assessed for therapeutic response at each visit and for 8 weeks thereafter for further response/clearance of warts					
At 2 weeks after dose - 1 (*n*=110)	0	99 (90)	5 (4.5)	2 (1.8)	4 (3.6)	Patients achieving complete clearance of warts received no further treatment
At 2 weeks after dose - 2 (*n*=92)	14	62 (67.4)	20 (21.7)	4 (4.3)	6 (6.5)	
At 2 weeks after dose - 3 (*n*=73)	13	33 (45.2)	22 (30.1)	7 (9.6)	11 (15)	
At 2 weeks after dose - 4 (*n*=54)	8	22 (40.7)	13 (24)	14 (25.9)	5 (9.3)	
At 4 weeks after dose - 5 (*n*=25)	24	7 (28)	5 (20)	1 (4)	12 (48)	Improvement continued during follow up period without treatment
At 8 weeks after Dose - 5 (*n*=13)	0	7 (53.8)	2 (15.3)	0	4 (30.7)	

Except for injection site pain, no adverse effects were noted in any of the patients

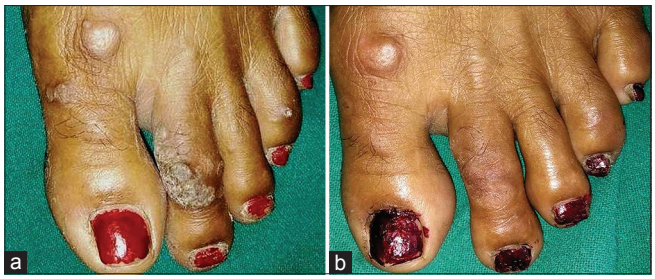

Figure 1: Multiple common warts over dorsal feet (a) before and (b) complete clearance of treated and other distant warts after five doses: The largest wart over second toe was treated with intralesional MMR vaccine

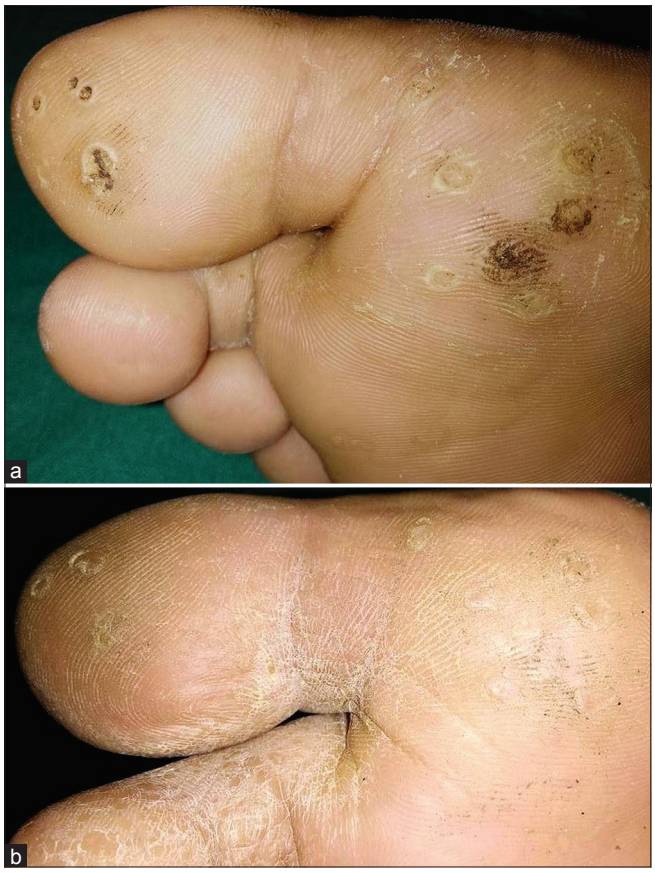

Figure 3: Multiple plantar warts (a) before and (b) after four treatment doses and before the fifth dose: The largest wart over ball of big toe was treated with intralesional MMR vaccine. Clearance of residual warts continued and they resolved completely at the end of study period

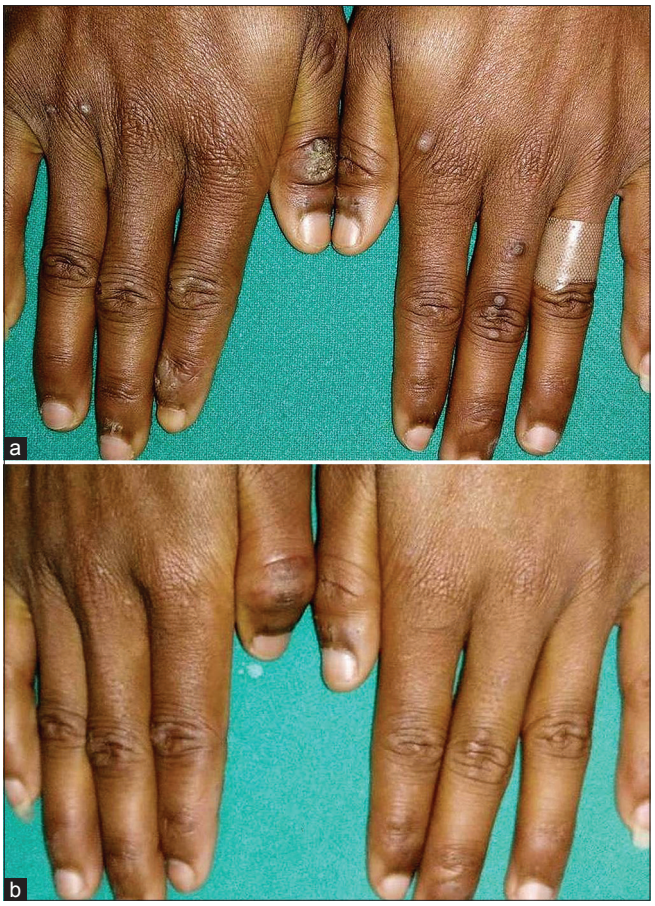

Figure 2: Multiple common warts over digits (a) before and (b) complete clearance of treated and other warts after five doses: The largest wart over thumb was treated with intralesional MMR vaccine

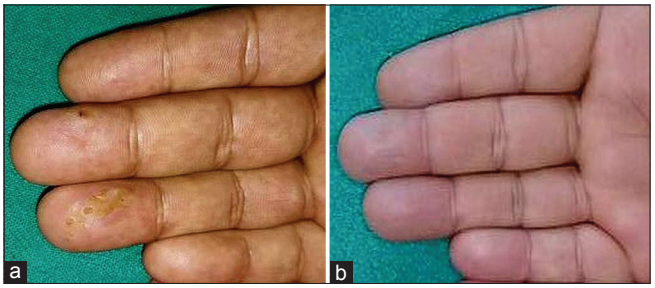

Figure 4: Multiple palmar warts over digits (a) before and (b) complete clearance of treated and other warts after five doses: The largest wart over middle finger was treated with intralesional MMR vaccine

warts with variable success rates.[8,9,11,12] Immunotherapy using intralesional MMR vaccine has been found useful in treating common warts particularly in children.[8-10] Nofal and Nofal[10] reported cure rates of 81.4% patients as compared with 27.5% in placebo group with intralesional MMR vaccine and antigens. Similar results were also reported by Mohamad *et al*.[13] and Zamanian *et al*.[8] separately observing complete clearance in 82%, partial response in 6%, and no response in 12% patients of plantar warts, and complete cure of common warts in 75%, relative cure in 16.66% and no cure in 8.33% patients, respectively. Na *et al*.[9] also observed decrease in size of warts in 51% of 136 patients, while complete resolution occurred in 5.6% of patients. Intralesional immunotherapy with MMR was superior with clearance rates of 80% and 40% with MMR, 60% with purified protein derivative, and 0% with saline in 10 patients each and to cauterization with 100% TCA in two separate studies, respectively.[14,15] Saini *et al*.[15] reported >75% improvement in 49.43% patients, whereas 26.44% patients had complete resolution from MMR immunotherapy, three doses of 0.3 mL intralesionally given at 2-week interval, for common warts over hands, feet, and soles. Comparatively, 11.11% had >75% improvement and

7.94% patients had complete resolution from TCA (100%) applied locally. Although 59 patients did not continue the treatment due to unsatisfactory response (Likert score 1), complete clearance of warts in 42 (82.4%) and good response in 2 (3.9%) of 51 patients who completed the study including those with lesions over dorsal hands and feet, soles, or periungual skin was observed in this study with one to five injections of MMR vaccine given as 0.25 mL per dose. This variable therapeutic outcome is perhaps from low dose used in this study that appears suboptimal in adults in comparison to children. However, there seems no consensus for a minimum dose of MMR vaccine, dosing frequency, and duration of therapy to treat warts.[8-10,13-20] Invariably, three to six doses of 0.–0.5 mL administered at intervals of 2–3 weeks have been used with outcome as varied [Table 4]. For instance, three doses

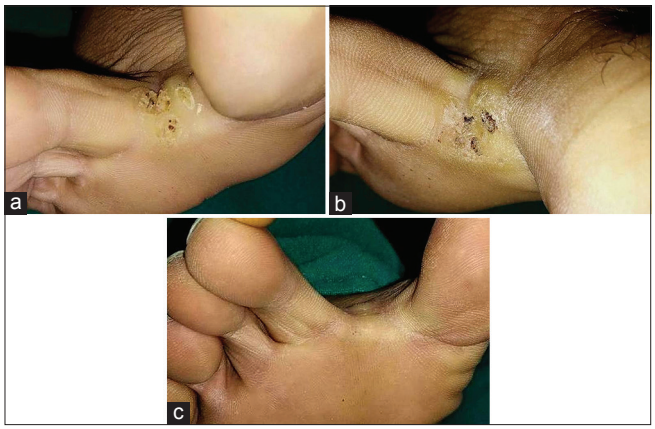

Figure 5: Multiple warts over first toeweb (a) before, (b) partial response after 3 doses, and (c) complete clearance of treated and other warts after five doses

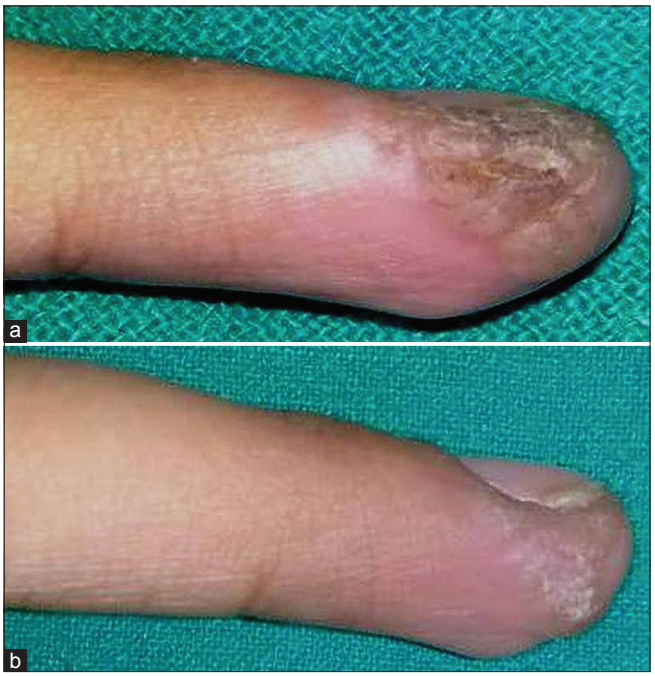

Figure 6: Periungual warts over ring finger (a) before and (b) after four treatment doses and before the fifth dose: Clearance of residual warts continued and they resolved completely at the end of study period

Table 4: Clinical trials of intralesional measles, mumps, rubella virus vaccine in immunotherapy of common warts

Reference and type of study	Patients	Treatment schedule	Results	Follow up, recurrences, adverse effects
Zamanian *et al*., 2014[8] Double blind randomized controlled study	MMR group - 30 patients Placebo group - 30 patients 24 versus 22 patients completed the study	MMR or saline 0.5 ml, I/L once in 2 weeks for 3 doses	Complete cure in 75%, relative cure in 16.7%, no cure in 8.3% patients as compared to 27.3%, 40.9%, 31.8% patients in saline group	Follow up: For 6 months after last injection Recurrence: Not known Adverse effects: Injection site pain 100% Flu-like symptoms in 30% patients of MMR group
Na *et al*., 2014[9] Open label study	136 patient	MMR 0.1-0.3 ml as per wart size, I/L once in 2 weeks till clearance or for 6 doses maximum	Complete resolution in 26.5% patients No response in 48.5% patients Partial response in 51.5% patients	Follow up: For 6 months after last injection Recurrence: In 5.6% patients Adverse effects: Injection site pain, pruritus and burning sensation in all
Nofal and Nofal 2010[10] Open label placebo controlled study	MMR group - 85 patients Placebo group-50 patients 70 versus 40 patients completed the study	MMR or saline 0.3 ml, I/L once in 2 weeks till clearance or for 5 doses maximum	MMR group - Complete response in 81.4%, partial response in 10% and no response in 8.6% patients as compared to 27.5% , 15% and 8.6% patients, respectively in saline group The difference was statistically significant	Follow up: Every 2 months for 6 months after last dose Recurrence: None Adverse effects: Injection site pain in 85.7% patients Flu-like symptoms in 8.6% patients

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Table 4: Contd...

Reference and type of study	Patients	Treatment schedule	Results	Follow up, recurrences, adverse effects
Mohamad *et al*., 2013[13] Open label controlled study	MMR group - 50 patients, Placebo group - 50 patients With plantar warts	MMR or Saline 0.3 ml, I/L once in 3 weeks till complete clearance or maximum of 3 doses	Complete response 82% versus 0%, Partial response 6% versus 30%, No response 12% versus 70% For distant warts Complete response 86% versus 0% Partial response 13.1% versus 0% versus no response in 100% patients in saline group	Follow up: Every month for 6 months Recurrence: Not known Adverse effects: Injection site pain (100%), Flu-like symptoms (4%) in MMR group
Shaheen *et al*., 2015[14] Open label controlled study	3 groups of 10 patients each	MMR, PPD 0.1 to 0.3 ml as per wart size, or Saline 0.3 ml, I/L once in 3 weeks till clearance or maximum of 3 doses	Cure rates - MMR group - 80% (treated wart) and 40% (distant wars) PPD group - 60% and Saline group - 0%	Follow up: Every 3 weeks for 3 months after last dose Recurrence: Not known Adverse effects: Erythema, swelling, vasovagal attack from MMR in 10% patients. Vasovagal attack in 10% controls
Saini *et al*., 2016[15] Open label controlled study	MMR group - 87 patients, TCA group - 63 patients	MMR 0.3 ml I/L or paring+TCA application at 2-week interval for 3 doses	>75% improvement in MMR 49.43% versus 11.11% in TCA group, complete resolution in MMR 26.44% versus TCA 7.94% group	Follow up: Once a month for 3 months after last dose. Recurrence: None Adverse effects: Injection site pain in 100% patients Flu-like symptoms, tenderness and postinflammatory pigmentation each in 1.15% from MMR Burning sensation in 100%, postinflammatory pigmentation in 3.17% patients in TCA group
*Gamil *et al*., 2010[16] Open label study	40 patients with plantar warts treated with I/L MMR (23 patients completed study)	0.5 ml I/L into largest wart every 3 week till complete clearance or maximum of 3 doses	Complete clearance in 87% Partial response in 4.3% No response in 8.7%	Follow up: For 9 months after last injection Recurrence: In 4.3% patients Adverse effects: Injection site pain in 82.6%, Flu-like symptoms in 4.3%
Nofal *et al*., 2015[17] Open label study	70 patients with ≥1 warts treated with I/L MMR (65 patients completed study	MMR 0.3 ml I/L into largest wart at 2 weeks till clearance or maximum of 5 doses	Complete clearance in 63% and 74.5% for distant warts Partial response in 23% No response in 14%	Follow up: Every month for 6 months after last injection Recurrence: In 4.8% patients Adverse effects: Injection site pain (100%), Itching (6.1%), Erythema (4.6%), edema (1.5%) Flu-like symptoms (12.3%)
Naseem and Aamir 2013[18] Open label study	170 patients with ≥1 warts treated with I/L MMR (150 patients completed study)	MMR 0.5 ml I/L into largest wart at 2 weeks till clearance or maximum of 3 doses	Complete clearance in 81.3% Partial response in 10% No response in 7.4%	Follow up: Every month for 6 months after last injection Recurrence: Not known Adverse effects: Injection site pain (100%), Flu-like symptoms (6.7%)

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Table 4: Contd...

Reference and type of study	Patients	Treatment schedule	Results	Follow up, recurrences, adverse effects
Raju *et al*., 2015[19] Open label study	30 patients with ≥5 warts treated with I/L MMR (27 patients completed study)	MMR 0.3 ml I/L into largest wart at 2 weeks till clearance or maximum of 5 doses	Complete clearance in 70.4% Partial response in 22.2% No response in 9%	Follow up: Every month for 6 months after last injection. Recurrence: Not known Adverse effects: Injection site pain (100%), Flu-like symptoms (6.7%)
Shah *et al*., 2016[20] Open label study	50 patients with≥1 warts treated with I/L MMR (10 patients had genital warts)	MMR 0.5 ml I/L into largest wart at 2 weeks till clearance or maximum of 3 doses	Complete clearance in 72% Partial response in 16% No response in 12%	Follow up: Every month for 6 months after last injection Recurrence: None Adverse effects: Injection site pain (36%), Flu-like symptoms (4%)

*Retracted article. MMR=Measles, mumps and rubella virus vaccine; I/L=intralesional; PPD=Purified protein derivative; TCA=Trichloroacetic acid

of 0.5 mL injected once in 3 weeks for up to three doses resulted in complete clearance in only 87% of plantar warts patients, whereas 5 intralesional doses of 0.3 mL given once in 2 weeks lead to complete resolution in only 63% of 65 patients in two separate studies.[16,17]

All patients in this study experienced injection site pain and swelling lasting for initial 1 or 2 days that did not warrant discontinuation of treatment. Itching, erythema, flu-like symptoms, or postinflammatory pigmentation, the commonly reported adverse effects of MMR vaccine, were not observed [Table 4]. There was no recurrence at the end of study period and cured patients rated their treatment very much satisfactory.

Limitations

Small number of patients, lack of placebo control group, and short follow-up are some of the limitations of this study.

Conclusion

Despite variable results intralesional MMR vaccine immunotherapy appears another possible and safe treatment option for common warts in a set of adult patients. Regression of untreated distant warts after single-lesion infiltration, no scarring or pigmentation as from destructive warts therapies, and possible low recurrence are some of the additional benefits. Few large well-designed, placebo-controlled studies for minimum effective dose and dosing schedule, and duration of the therapy that make the treatment regimen effective are highly desirable for making any recommendation. However, incomplete therapeutic response in the short term may lead to dissatisfaction and poor treatment compliance. Other possible reasons for high dropout could be long duration of treatment, slow response to immunotherapeutic agent, injection site pain, or easy access to internet-based information for more effective and rapid therapeutic modalities.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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